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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/537,356	06/03/2005	Klaus Dietzel	26794U	2653

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EXAMINER	
JEAN-LOUIS, SAMIRA JM	
ART UNIT	PAPER NUMBER
1627	
MAIL DATE	DELIVERY MODE
01/14/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/537,356	DIETZEL ET AL.	
	Examiner	Art Unit	
	SAMIRA JEAN-LOUIS	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *6-11,13-17 and 25-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-11, 13-17, and 25-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Arguments

This Office Action is in response to the amendment submitted on 10/21/09. Claims 6-11, 13-17, and 25-30 are currently pending in the application, with claims 1-5, 12, and 18-24 having being cancelled. Accordingly, claims 6-11, 13-17, and 25-30 are being examined on the merits herein.

Receipt of the aforementioned amended claims is acknowledged and has been entered.

Applicant's argument with respect to the Arguments of fixed combination presented in the Non-Final Office Action dated 05/22/09 has been fully considered but is not found persuasive. The Examiner again reiterates the fact that the claims as presented before such Office Action was issued did not recite the limitation of a fixed combination of ciclesonide and formoterol. In fact, the claims previously recited that ciclesonide and formoterol were in "free combination" and were present in "separate pack units". As a result, the Examiner contended that applicant could not argue limitations that were not previously present. Therefore such arguments were rendered moot.

As for applicant's arguments regarding Calatayud, the Examiner refers applicant to the Non-Final Office action on page 14 as to why Calatayud was being provided. While the Examiner erroneously delineated that Calatayud taught formoterol (as

opposed to ciclesonide), the Examiner maintains that the rejection clearly delineated the teachings of Calatayud which taught that "ciclesonide" and its epimers possess strong anti-inflammatory properties and high therapeutic index. As a result, Calatayud provides the motivation as to why one of ordinary skill in the art would select the R-epimer of "ciclesonide" to treat airway diseases.

Applicant's argument with respect to the 112, first paragraph rejection has been fully considered. Given that applicant has removed the non-enabling terms and amended the claims, such rejection is now moot. Consequently, the rejection of claims 6-11 and 13-17 under 35 U.S.C. 112, first paragraph is hereby withdrawn.

Applicant's argument that Magee in view of Calatayud does not establish a proper case of *prima facie* obviousness has been fully considered. Applicant further contends that present claim 6 (i.e. amended claim 6 as of 10/21/09) is directed to a pharmaceutical composition comprising a fixed combination of active compounds consisting of the active compound ciclesonide or an epimer thereof and the active compound R,R, formoterol or a salt, or hydrate of a salt thereof, wherein the active compounds are in a ready mixed fixed combination whereas Magee does not teach such combination. Such arguments are however not found persuasive as the Examiner continues to maintain that Magee in view of Calatayud still render obvious applicant's invention. While applicant claims a fixed combination consisting of ciclesonide and formoterol and further claims that only two active compounds are included in the

aforementioned composition, the Examiner respectfully fully points out that the claims are directed to a pharmaceutical composition "comprising" a fixed combination of the active compounds ciclesonide and formoterol. Such recitation in no way excludes addition of other active ingredients. Contrary to applicant's belief, such recitation solely requires that the "fixed combination" only contains ciclesonide and formoterol but this in no way prevents addition of other ingredients including addition of active compounds to the pharmaceutical composition. Instead, applicant would need to further recite in the claims that ciclesonide and formoterol are the only two active ingredients in the composition.

Nonetheless, the Examiner maintains that given that Magee teaches compositions for the treatment of airway diseases such as COPD, asthma, chronic bronchitis, etc...comprising PDE4 inhibitors in combination with one or more active ingredients including ciclesonide and formoterol, the Examiner contends that Magee in view of Calatayud does indeed render obvious applicant's invention. Moreover, given that Magee teaches that the PDE4 inhibitors can be co-administered with the aforementioned compound as a single dosage with the aforementioned compounds or apart from the other components, the Examiner maintains that such disclosure still reads on applicant's amended claims. Additionally, because of the presence of the term "comprising" in the amended claims, the Examiner contends that PDE4 inhibitors are not excluded out of the aforementioned composition but rather such inhibitors cannot be part of the fixed combination. Again, Calatayud was provided to demonstrate the use of particular epimers of ciclesonide in pharmaceutical compositions especially that of the

R-epimer of ciclesonide which possesses high anti-inflammatory properties and high therapeutic index. As a result, the Examiner maintains that Magee in view of Calatayud does indeed render obvious applicant's invention and the rejection is therefore maintained.

Applicant's argument with respect to Keller who does not teach the fixed combination of the instant invention has been fully considered but is not found persuasive. The Examiner again reiterates the fact that despite the amended claim language of "consisting of", this in no way excludes addition of other ingredients. Because Magee teaches co-administration of PDE4 inhibitors in combination with ciclesonide and formoterol as a single dosage or apart from the combination and in view of Calatayud who teaches that the R-epimer of ciclesonide possesses high therapeutic index, the examiner contends that one of ordinary skill in the art would have found it obvious to administer the compounds of Magee in view of Calatayud for the treatment of airway diseases since Magee teaches that such compounds are effective in treating various airway diseases including asthma, COPD, and chronic bronchitis. Keller, on the other hand, was provided to demonstrate that compositions containing formoterol can be combined with ciclesonide and excipients such as magnesium stearate can be added to such compositions to improve the resistance to moisture. In fact, Keller further teach addition of carriers such as lactose monohydrate further supporting the notion that Keller in view of Magee and in further view of Calatayud still renders obvious applicant's

invention. As a result, the Examiner maintains that the rejection of claims 6-11 and 13-17 in view of Keller, Magee and Calatayud is indeed proper.

For the foregoing reasons, the 112, first paragraph rejection is withdrawn while the rejections of record under 103 (a) remain proper and are maintained. However, in view of applicant's amendment, the following modified 103 (a) Final rejections are being made.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 6-11, 13-17, and 25-30 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Magee et al. (2002/0111495 A1, previously submitted) in view of Calatayud et al. (U.S. 5,482,934, previously submitted).

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any

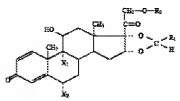
inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Magee et al. teach compounds of formula I useful as inhibitors of PDE4 in the treatment of diseases especially asthma, chronic bronchitis, and chronic obstructive pulmonary disease (abstract and pg. 1, paragraph 0006). Magee et al. further teach that the compounds may be made in a composition together with a pharmaceutical carrier for treating a number of diseases including bronchitis, obstructive bronchitis, COPD, allergic asthma and bronchial asthma (instant claims 11 and 15; see pg. 32, paragraphs 0190-0194). Magee et al. further teach the combination of a compound of formula I together with one or more therapeutic agents including formoterol and ciclesonide (instant claim 6; see pg. 34, paragraph 0218, and pg. 98, paragraphs 0620, 0630, and 0636). These compounds and therapeutic agents are administered to a patient in combination with the compounds of formula I wherein the compounds or components are formulated together (i.e. fixed combination) into a single dosage form or PDE4 inhibitors are formulated apart from the other components and which releases the components and compounds at substantially the same time (instant claims 6 and 11; see pg. 92, paragraphs 0571-0572 and pg. 99, paragraph 0671). The compounds and therapeutic agents according to Magee et al. may be in the form of salts or acid

salts including acetate, citrate, fumarate, gluconate, hydrochloride, hydrobromide, nitrate, sodium phosphate, stearate, sulfate, sulfosalicylate and tartrate (instant claims 9-10; see pg. 99-100, paragraphs 0672, 0674 and 0676) and may be administered in various dosages and follow various treatment regimen depending upon a variety of factors including drug combination, age, body weight, general health, sex, diet, time of administration, rate of excretion, physician's judgment and severity of the disease (instant claims 11, 16-17; see pg. 99, paragraph 0671). Additionally, Magee et al. teach that sugars may be added to impart a variety of desired characteristics to the pharmaceutical compositions and include lactose, glucose, galactose, and combinations thereof (e.g. since lactose monohydrate is a combination of glucose and galactose such recitation clearly reads on claims 27 and 30; instant claims 25-30; see pg. 102, paragraph 0697). Finally, Magee et al. teach that the pharmaceutical composition may be administered by nasal aerosol or inhalation through the use of a dry powder inhaler (instant claims 6, 11 and 14; see pg. 104, paragraphs 0709 and 0719).

Magee et al. do not specifically teach the R-epimer of ciclesonide in an amount greater than 95% in the pharmaceutical composition.

Calatayud et al. teaches compounds of the general formula



with X1 an X2 corresponding to H and R1 is a phenyl group and R2 represents radicals such as C=OCH(CH3)CH3 in the form of an R epimer, S epimer or mixture of the R and S epimers (i.e. ciclesonide) as drugs and/or therapeutic agents (see abstract and col. 3, lines 1-61). Calatayud et al. further teach that these compounds possess intense pharmacological activity with no or minimal systemic effects (see col. 2 lines 21-23, col. 15, lines 10-11 and col. 16, lines 27-30). Calatayud et al. also teach synthesis of the mixture of ciclesonide with both the R and S epimers which are then further purified to obtain either of the epimers in a proportion of at least 99.9% (see col. 11, lines 21-61 and col. 17-18, table II, compound 9). Importantly, Calatayud et al. teach that the R-epimer of ciclesonide possesses high anti-inflammatory activity, high glucocorticoid activity and high therapeutic index (see col. 17-18, table 3, compound 9).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the R-epimer of Calatayud into the composition of Magee et al. to treat airway diseases since Calatayud et al. teach that the R-epimer possesses intense glucocorticoid activity with minimal systemic effects. Given that Magee et al. teach a pharmaceutical composition co-administered with compounds of formula I and ciclesonide and formoterol, and Calatayud et al. teach R-epimers of ciclesonide with high glucocorticoid activity, anti-inflammatory activity and minimal systemic effects, one of ordinary skill would have been motivated to incorporate the R-epimer of ciclesonide into the composition of Magee et al. with the reasonable expectation of providing a

pharmaceutical composition that is efficacious in treating airway diseases and a composition that is readily absorbed with no systemic effects.

Claims 6-11, 13-17, and 25-30 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Keller et al. (U.S. 6,645,466 B1, previously submitted) in view of Magee et al. (2002/0111495 A1, previously submitted) and in further view of Calatayud et al. (U.S. 5,482,934, previously submitted).

The Magee and Calatayud references are as discussed above and incorporated by reference herein.

Keller et al. teach dry powder formulations for inhalation (i.e. instant claim 6) containing a pharmaceutically effective carrier, pharmaceutically active compounds and magnesium stearate (see abstract and col. 4, lines 55-67). Keller et al. further teach that the magnesium stearate is added to dry powder formulations which contain a beta mimetic in the form of salt such as formoterol fumarate or formoterol tartrate (instant claims 9-10), and/or an anticholinergic and/or a corticosteroid including ciclesonide (instant claim 6; see col. 6, lines 52-64 and col. 7, lines 5-10). The amount of active compounds in the formulations can vary within wide ranges or from 0.1-10% though the exact volumetric dosage can be determined depending on the desired dose (instant claim 16; see col. 7, lines 12-39). Additionally, Keller et al. teach that the magnesium stearate which is added to the composition helps improve resistance to moisture and is

present along with the therapeutic compounds in the form of interactive mixtures (i.e. ready mixed; see col. 2, lines 5-8; col. 4, lines 62-65 and col. 5, lines 1-8). Keller further teaches single dosage administration wherein the magnesium stearate is mixed together with the active ingredients in any desired sequence or wherein the magnesium stearate mixed separately and then the active compounds are admixed in the magnesium stearate mixture (see col. 8, lines 46-65). Moreover, Keller teaches that pharmaceutical carriers can be added including lactose monohydrate (instant claims 25-30; see col. 7, lines 23-67; col. 8, lines 1-16, and col. 15, claims 5-6).

Keller et al. do not specifically teach a method of treating airway diseases or the addition of the R-epimer of ciclesonide into the composition.

As previously stated, Magee et al. teach pharmaceutical composition for the treatment of airway diseases including asthma and COPD containing compounds of formula I along with ciclesonide and formoterol where they are administered together (i.e. fixed combination) into a single dosage form which releases the components and compounds at substantially the same time (instant claims 6, 11, and 15; see pg. 92, paragraphs 0571-0572 and pg. 99, paragraph 0671). Moreover, Magee et al., also teach that these agents may be administered in various dosages and follow various treatment regimen depending upon a variety of factors (instant claims 11, 16-17; see pg. 99, paragraph 0671).

Calatayud et al. teach synthesis of the mixture of ciclesonide with both the R and S epimers and which are then further purified to obtain either of the epimers in a proportion of at least 99.9% (see col. 11, lines 21-61 and col. 17-18, table II, compound 9). Importantly, Calatayud et al. teach that the R-epimer of ciclesonide possesses high anti-inflammatory activity, high glucocorticoid activity and high therapeutic index (see col. 17-18, table 3, compound 9).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to substitute the R-epimer of Calatayud et al. into the composition of Keller et al. since Calatayud et al. teach that the R-epimer of ciclesonide possesses high anti-inflammatory activities. Likewise, it would have been obvious to one of ordinary skill in the art at the time of the invention to vary the treatment regimen as taught by Magee et al. and use the aforementioned composition for the treatment of airway diseases since Magee et al. teach the same type of composition for the treatment of asthma and COPD. Given that Keller teaches dry powder inhaler moisture-resistant compositions containing ciclesonide and formoterol or their salts, and Magee et al. teach pharmaceutical composition containing compounds of formula I along with ciclesonide and formoterol for the treatment of airway diseases including asthma and COPD, and Calatayud et al. teach R-epimers of ciclesonide with high glucocorticoid activity, anti-inflammatory activity and minimal systemic effects, one of ordinary skill would have been motivated to incorporate the R-epimer of ciclesonide into the composition of Keller et al. and further used such composition for the treatment of

airway diseases as taught by Magee et al. with the reasonable expectation of providing a pharmaceutical composition that is efficacious in treating asthma and COPD and a composition that produces no systemic effects.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

01/06/2010

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627